

### ***Remarks***

Applicants have carefully considered this Application in connection with the Examiner's Action and respectfully request reconsideration of this Application in view of the following remarks.

#### ***I. Telephone Interview***

The Examiner granted a telephone interview on 1 April 2009 to discuss the outstanding rejection of record under 35 U.S.C. §103(a). Applicants thank the Examiner for the courtesy of the interview. In the Office Action, the Examiner had stated that an amendment to claim 1 replacing "comprises" with "consisting of" would overcome the rejection. During the interview, the Examiner stated that paragraph [0393] of the Doi reference teaches that DNK333 is a dual NK<sub>1</sub>- NK<sub>2</sub> antagonist and may be administered alone, and as a result, such an amendment would not overcome the rejection.

#### ***II. Rejection under 35 U.S.C. § 103(a)***

The Examiner has rejected Claims 1-8 under 35 U.S.C. §103(a) as being unpatentable over U.S. 2004/0058914 ("Doi"). Applicants respectfully traverse this rejection.

Applicants have discovered that compounds of formula I in Claim 1 can be used to treat urinary incontinence. Applicants claim methods of treating urinary incontinence by administering such compounds.

The Examiner stated in the Office Action that Doi teaches the administration of the neurokinin receptor antagonist DNK333 (the compound of Claim 7 in the present application) in the treatment of urinary incontinence. (See Office Action, p. 2.) As noted above, the Examiner stated in the telephonic interview on 1 April 2009 that Doi teaches at paragraph [0393] that DNK333 is a dual NK<sub>1</sub>- NK<sub>2</sub> antagonist and may be administered alone. (See the Interview Summary of the telephonic interview.) In the Office Action at page 2, the Examiner also refers to paragraph [0506] in Doi, which is

part of the sentence that begins in paragraph [0505] of Doi. Paragraphs [0505] and [0506] of Doi read as follows:

[0505] By the combined use of an NK<sub>1</sub>-receptor antagonist (particularly compound (I) or a salt thereof or a prodrug thereof) and an anti-cholinergic drug or NK<sub>2</sub>-receptor antagonist, [0506] (1) a superior treatment effect of the diseases such as urinary frequency, urinary incontinence, asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, osteoarthritis, pain, cough, irritable bowel syndrome, emesis, depression, anxiety, manic depression psychosis, schizophrenia and the like can be exerted.... (Emphasis supplied.)

However, this is an unsubstantiated claim of efficacy with respect to all of the 14 specifically cited diseases and conditions, including urinary incontinence. There is no experimental evidence in Doi to support this claim. With respect to all of cited diseases and conditions except purportedly for urinary incontinence, there is no experimental evidence whatsoever in Doi. With respect to urinary incontinence, as set forth in the previously submitted Declaration of Eckhard Weber under 37 C.F.R. § 1.132 (the "Declaration"), Doi does not demonstrate that any of the compounds disclosed in Doi are effective to treat urinary incontinence. (See Declaration, paragraph 4).

The only experimental data in Doi that purports to demonstrate the effectiveness of the disclosed compounds in treating urinary incontinence are in Experimental Examples 1 and 2. (See Declaration, paragraph 4). However, that experimental data instead demonstrates the effectiveness of a combination of disclosed compounds in increasing cyclophosphamide-impaired bladder capacity. (See Declaration, paragraph 4). As set forth in the Declaration, the model used in Experimental Examples 1 and 2 that purportedly tested for the efficacy of a composition with respect to urinary incontinence was based on the treatment of animals under a urethane anesthesia with cyclophosphamide. Instead of testing for the efficacy of a composition with respect to urinary incontinence, the model tested for the efficacy of a composition with respect to increasing bladder capacity. (See Declaration, paragraph 4). As also set forth in the Declaration, the model used in Doi is a model for cystitis, which is an inflammatory condition. (See Declaration, paragraphs 5 and 6.) If inflammation plays a role in urinary

incontinence, it is a minor role. (See Declaration, paragraph 6.) As a result, the model used in the Doi reference is a model that is not directed towards a neuromuscular mechanism for urinary incontinence and is not a model for urinary incontinence. (See Declaration, paragraph 6.)

As pointed out in the Declaration, the Experimental Examples in Doi demonstrate that an NK<sub>1</sub> receptor antagonist alone is not effective in treating the condition present in the model employed (see Declaration, paragraph 7) and only teach combination therapy as being effective to treat that condition (see Declaration, paragraph 10). One of the articles referred to in the Declaration is Green, et al., "Efficacy and Safety of a Neurokinin-1 Receptor Antagonist in Postmenopausal Women with Overactive Bladder with Urge Urinary Incontinence," The Journal of Urology, Vol. 176, pp. 2535-2540 (2006). A copy of that article was attached to the Declaration. In the Green article, the results from a clinical trial where an NK<sub>1</sub> receptor antagonist alone was used to treat urinary urge incontinence are presented. The Green article states that the clinical trial demonstrated the efficacy for an NK<sub>1</sub> receptor antagonist in urge urinary incontinence (see page 2538). If the Experimental Examples in Doi purport to show efficacy for the treatment of urinary incontinence, then why are the experimental results from those Experimental Examples inconsistent with the clinical trial results reported in the Green article? The reason is clear: the model used in Doi is not a model for urinary incontinence. (See Declaration, paragraph 7.)

This inconsistency between the teachings of the Green article and the results of the Experimental Examples in Doi would lead one of ordinary skill in the art to at least question the accuracy of the unsubstantiated claim in Doi about the efficacy of the recited compounds in Doi, whether used alone or in combination, in treating urinary incontinence or to even conclude the claim was false. As a result, contrary to what is stated by the Examiner on page 3 of the Office Action, one of ordinary skill in the art would not "have been motivated to administer any among the recited compounds with a reasonable expectation of success." Furthermore, based on the experimental data provided by Doi, one of ordinary skill in the art could not conclude from such

experimental data that a compound according to formula I of present Claim 1 would be effective in the treatment of urinary incontinence. (See Declaration, paragraph 10.)

In contrast to the model used in Doi and the experimental results in Doi, the models used by the Applicants are models for non-inflammatory overactive bladder/urinary incontinence and the experimental results in the Specification demonstrate preclinical efficacy of the compounds of formula I of present Claim 1 for the treatment of urinary incontinence. (See Declaration, paragraph 9.) This is in stark contrast to Doi which does not provide any experimental evidence demonstrating that any of the compounds disclosed in Doi are effective to treat urinary incontinence. (See Declaration, paragraphs 4 and 10.)

The experimental preclinical data in the Specification are consistent with the clinical trial findings of the Green article and are further evidence that the Applicants' models are models for urinary incontinence. Furthermore, the authors of the Green article state that to their knowledge, "this is the first clinical trial to demonstrate the efficacy for an NK<sub>1</sub> receptor antagonist in [urge urinary incontinence]." (See page 2538 of the Green article.) In view of Doi not providing any experimental evidence that the compounds disclosed in Doi are useful for the treatment of urinary incontinence and it being several years after the Applicants' invention when the Green article was published in December 2006 with clinical trial data demonstrating the efficacy of an NK<sub>1</sub> receptor antagonist in the treatment of urinary incontinence, Applicants' discovery that compounds according to formula I of present Claim 1 can be used to treat urinary incontinence was both novel and unexpected at the time of Applicants' invention.

Since Doi does not provide any experimental evidence that the compounds disclosed in Doi are useful for the treatment of urinary incontinence, either alone or in combination, the experimental evidence in Doi at a minimum would lead one of ordinary skill in the art to question the validity of the claim made by Doi about the efficacy of the disclosed compounds in treating urinary incontinence, and the Green article with clinical trial data demonstrating the efficacy of an NK<sub>1</sub> receptor antagonist in the treatment of urinary incontinence was not published until several years after the Applicants' invention, the claimed inventions of Applicants are patentable over Doi.

**III. Conclusion**

In view of the foregoing, Claims 1-8 are in condition for allowance, and Applicants earnestly solicit a Notice of Allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this Application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration to this Reply is respectfully requested.

Respectfully submitted,  
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